CHAPTER IX: GLYCAN-BASED NATURAL PRODUCTS

So, the way that I'm going to do that today is to first provide you a context and a framework of what I call is glycan-based natural products. Glycan, the word also is used for carbohydrates. And, I'm going to come back to that in greater detail. And, I think an important point that needs to be emphasized right at this time is the fact that they are complex. In many ways, you can view these as molecules that truly represent the complexity of, in terms of not only their chemical properties, but how their chemical properties, in may sense, translate into function.

So, obviously, I want to put this in the context of the importance of glycans, the point that I made a few seconds ago, the fact that they have, in many ways, fundamentally changed the central dogma of molecular biology, in the sense that the dogma has been revisited in the context of the role of these glycans in regulating biological functions. And, needless to say, many, many products in the market, and, particularly, natural products, are glycan based. And, I'm going to sort of give you a sense of what it means, and how to really think about this problem, and how we went about looking at it.

Obviously, one of the important things that become central to our ability to understand the structure function relationship of these kinds of molecules, is the tools and techniques that could be used to unravel or demystify the complexity of these molecules and the technologies, which I'm calling glycol technologies, inherent issues and challenges with the technologies to be able to access these kinds of molecules, and how we went about, and when I meant we, I would be using examples that my own lab spent time on doing. But, also, I would be bringing other examples from the field, to basically illustrate the challenges and how accessing the complexity of these molecules was eventually achieved through a set of different technologies that got us to look at structure function relationship.

And, what I'd like to do is the following. Touch upon three examples. Heparin, which belongs to the larger family of complex polysaccharoids, called glycol __________ glycan, where chondroitin is an example, too. And, through heparin, I'll sort of illustrate some of the overall concepts of what you could view as perhaps the most complex of these carbohydrate polymers, and how the structure active __________ paradigm has really been approached with regard to some of the recent technologies, to be able to get to not only the basic mechanistic studies, but some of the clinical applications.

Obviously, I'm going to focus on another different class of molecules, just to give you a flavor of when carbohydrates are attached to small molecules, such as in ginseng, what are some of the key issues that become important to not only understand the structural aspects of these molecules, but the consequence, in terms of biological function.

A very different kind of complex polysaccharide derived from plants, pectin, is another very interesting example, again, a natural product, people have been exploring the different clinical applications of pectin. I'm going to touch upon the structural aspects of it, and how the structural leads to function from a mechanistic point of view.

And, what I'm then going to do is to use these three examples in terms of what we have learned more fundamentally, with regard to complex carbohydrates, and tell you how that has shaped our thinking in a new area, what I call as integrated approach to therapeutics, that is getting to the understanding of the mechanism of these molecules, releverage nanotechnology to come up with newer approaches for treating cancer. And, I'll end my talk with sort of highlighting some of the thinking that went into it, and where we are with regard to a design of a novel strategy, which I call is the integrated approach to therapeutics in cancer. And, then, of course, I'll end with a summary.

So, with that, let me begin with first addressing the issue of what are glycans and why should it be relevant to this audience, and how that relevance eventually bridges into something more significant, in terms of their complexity.

I think all of us are familiar with this aspect of carbohydrates, the fact that they provide energy, coming from various different sources. And, of course, there's a lot of excitement in looking at the sources of carbohydrates from the point of in a better food, organic food, and how to balance, if you will, the ying and yang of getting the right amount of carbohydrate. With, of course, the different kinds of diets, the Atkins diet and so on and so forth.

But, underlying that is the fact that, essentially, carbohydrates provide energy. And, much of the earlier work in carbohydrates essentially focused on how carbohydrates, with fat, and, of course, proteins, go through distinct biochemical steps, including the TCA cycle, as a way to generate the energy currency which eventually leads to cells to function. And, of course, we all do know that there's nine calories per gram from fat, but only four from carbohydrates. Very simply put, carbohydrates is the easier currency. It takes a lot more carbohydrates to generate energy as against fat. But, it's one that, if it's not used the right way, it could eventually lead to production of fat and the storage of fat. And, much of the historical appreciation of carbohydrates focused on the biochemical pathways of how carbohydrates played a role in energy metabolism.

But, what I'm going to talk about today is, while we began from there in understanding this set of molecules, they do a lot more than provide energy. While energy is, obviously, a very basic and a fundamental process, I'm going to now put glycan in a much broader context of biological systems, and then get to the heart of the structure function relationship and try to really give you a flavor for that, in terms of the biological systems.

So, we're all aware of the fact that, from the point of view of energy, there are several different kinds of carbohydrates which historically have classically been known as the storage molecules, like glucose, fructose, sucrose, a variety of simple carbohydrates, but they are polemic in nature, units that repeat themselves in a chain and how they are broken down.

Now, when we look at the role of these molecules, in terms of where they are found and present, they pretty much are present from plants to, you know, insects, to animals. And, the complexity goes up. The complexity goes up in terms of how these basic chains are decorated with functional modifications, and how those functional modifications become very important, in terms of the biological modules they modulate.

So, going beyond the storage, when you're looking at structural polysaccharides, such as cellulose, which is the key polysaccharide for plants. It provides the architecture for the plant, for instance, which provide the shell for insects. That's the structure polysaccharide for insects. You begin to see some of the modifications and the complexity that start building in these molecules, how they assemble together.

Now, when you go beyond that, and I want to illustrate with pectin, since I'm going to come back to pectin as an example, you have a polymer, but then you have regions of these molecules that have enormous chemical diversity, various different building blocks. Not only do you have a linear molecule here, but they branch out, and you have a combination of linear and branch structures that lead to the complexity. They're found in the roots, they're found in the fruits, they're found to be not only important structural parts, in some sense, at least historically, as they were viewed, but they do play a central role in the cell to cell communication of plants. And, plant biology has really taken off dramatically in trying to understand the role of these pectins in cell to cell communication.

Just recently, they've been able to access a variety of enzymes that make these pectin-like molecules, to truly understand what eventually leads to this complex biosynthesis. And, I'm going to come to this in the context of minili polysaccharides so that you begin to understand what are some of the fundamental issues and challenges when you're looking at an assembly of such a complex, and how does such a complex get to the place where it's supposed to be assembled, and regulate function.

Now, I do not want to lose sight, when you're looking at plant, there's a whole class of molecules, ginseng molecules from neen[?] and similar products, where small molecules, or small molecular active components have various sugar moieties to it. Simple glucose, manosis, modified carbohydrate structures, and, fundamentally, it is thought that their role is to either provide solability, provide specificity for structure. And, sometimes, even targeting. And, we're just beginning to scratch the surface of this space. Because, trying to access these molecules by themselves, given that, as if you choose ginseng as an example, they're complex mixtures. They're not just one product. They're several chemicals that are present in this mixture. And, part of the challenge is to really tease apart the ratios of these mixtures, and how each of these components play a different role in terms of biological function. And, when I talk about ginseng, I will come back to address some of these issues.

So, changing gears, if you look at complex polysaccharides in mammalian system, the example that I show with this picture, it's an electron micrograph of a section of the human cartilage. It's essentially made of both this family of molecules that I mentioned, glycol semi glycan, and specifically that one of that most of you in this audience might know, which is chondroitin sulfate. It is the largest polysaccharide component of the cartilage, and these ant like structures essentially, if you zoom in here, here's a protein with various carbohydrate chains radiating out of these protein, and there is a sense that these molecules play a role in hydrating the micro environment of the cartilage, solubilizing a variety of different molecules, and, by the large, the notion is they play a structural role. And, what I'm going to go through in the next few slides is to tell you that that's just the tip of the iceberg. These molecules, they're chemically diverse, but the functional groups, in terms of the basic backbone chain, dramatically regulate several biological processes, and I'll expand on that.